REMARKS

Status of the claims

Claims 25 - 38 and 40 - 77 are pending and have been examined.

Claims 25, 35 - 37, 40, 47, 57, 58 and 75 are amended herein. Claim 55 is canceled herein. New claim 78 is added herein.

Claims 25 - 38, 40 - 54, and 56 - 78 are presented for further examination.

Objections to the Specification

The objection to the specification's embedded hyperlink has been obviated by amendment and should be withdrawn.

Objections to the Claims

Claim 50

The Examiner objects to claim 50 for including "stem cell" among the cells recited in its Markush group, on grounds that claim 25, from which claim 50 indirectly depends, affirmatively excludes "stem cells".

The objection is in error.

Solely to satisfy current political policy, and without having acceded to the propriety of the Examiner's having required such limitation, claim 25 was previously

amended to recite that the cells in which nucleic acids are targeted for sequence alteration are "not human ***embryonic*** stem cells" (emphasis added).

This exclusion is not as broad as the Examiner has asserted. Accordingly, claim 50 may still list "stem cells" among the cell types recited in its Markush group: incorporating "all limitations" of claim 25 pursuant to 37 C.F.R. § 1.75(c), the method of claim 50 may be practiced with all human stem cells that are not human ***embryonic*** stem cells, including, *e.g.*, human hematopoietic stem cells.

Applicants respectfully request that the objection be withdrawn.

Claim 55

Objection to claim 55 has been obviated by cancellation of the claim.

Rejections under 35 U.S.C. 112, ¶ 2, Have Been Obviated by Amendment and Should be Withdrawn

Rejections of claims under 35 U.S.C. § 112, ¶ 2 have been obviated by amendment and should be withdrawn.

Scope of Enablement Rejections under 35 U.S.C. 112, ¶ 1, Have Been Obviated By Amendment And/Or Are In Error And Should be Withdrawn

Recognizing that applicants' specification enables "[a] method of targeted sequence alteration of a nucleic acid present in a cell in culture or in a cell-free extract," Office Action at 4, item 13, the Examiner nonetheless maintains that applicants' specification does not enable targeted sequence alteration of a nucleic acid present in selectively enriched cells present *in vivo*, motivating a scope of enablement rejection. The Examiner further suggests that the rejection may be obviated by limiting the claims "to a method using a cell in culture/in vitro".

The rejection is factually in error: applicants' claimed methods are indeed enabled to the full scope of the claim as examined.

However, business exigencies demand that applicants' *ex vivo* programs be afforded patent protection as soon as practicable.

Accordingly, applicants will not here present the available evidence to prove the factual inaccuracy of the Examiner's statements. Without acceding to the rejection, and solely to expedite prosecution, applicants have amended the claim pursuant to the Examiner's suggestion, obviating the rejection, which should be withdrawn. Applicants reserve the right to prosecute a claim of the examined scope in one or more

continuation applications, at which time applicants will have the time to adduce further factual evidence in support of the full scope of applicants' claims.

In a second scope of enablement rejection, the Examiner argues that, to the extent that claims 26, 50, and 72 encompass making a targeted nucleic acid alteration in a stem cell, including a human hematopoietic stem cell, "[t]he only contemplated use for making genetic alterations in stem cells (and hematopoietic stem cells) is for stem cell therapy. However, the claims are not enabled for stem cell therapy. . . ." Office action at 5.

Applicants do not here claim methods of stem cell therapy.[1] What applicants claim is a "method of targeted sequence alteration of a nucleic acid present within selectively enriched cells in vitro, cells in culture, or cell-free extracts." As to *this* invention -- which is indeed the *only* invention as to which the Examiner may properly offer rejections -- the Examiner has himself stated on the record that applicants' specification enables *that* invention across the entirety of the claimed scope.

The rejection is manifestly improper and should be withdrawn.

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[1] Applicants may indeed so claim in a later continuation or divisional application, and respectfully traverse the Examiner's assertion that applicants' specification fails to enable such methods. But that issue is not properly before the Examiner in the present case.

Rejections Under 35 U.S.C. § 103 Are in Error and Should be Withdrawn

Claims 25 - 38 and 40 - 69 are variously rejected as having been obvious under 35 U.S.C. § 103 over three separate combinations of references. Claims 70 - 77 are free of art rejection.

Yamamoto in View of Meyer

In a first rejection under 35 U.S.C. § 103, the Examiner rejects claims 25 - 38, 40 - 58, and 63 - 69 over Yamamoto in view of Meyer. Claims 59 - 62 and 70 - 77 are free of this rejection.

It is by now well settled that the Examiner must show a motivation to combine references to establish a *prima facie* case of obviousness. *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998); *In re Dembiczak*, 50 USPQ2d 1614 (Fed. Cir. 1999); *WMS Gaming Inc. v. International Game Technology*, 51 USPQ2d 1385 (Fed. Cir. 1999); *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 56 USPQ2d 1456 (Fed. Cir. 2000); *In re Lee*, 61 USPQ2d 1430 (Fed. Cir. 2002). "There is no suggestion to combine . . . if a reference teaches away from the combination. . . ." *Tec Air, Inc. v. Denso Manufacturing Michigan Inc.*, 192 F.3d 1353, 52 USPQ2d 1294, 1298 (Fed. Cir. 1999).

Additionally, "[a] *prima facie* case of obviousness can be rebutted if the applicant ... can show `that the art in

any material respect taught away' from the claimed invention." *In re Geisler*, 43 USPQ2d 1362, 1365 (Fed. Cir. 1997) (quoting *In re Malagri*, 182 USPQ 549, 533 (CCPA 1974)). "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, ... would be led in a direction divergent from the path that was taken by the applicant." *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 52 USPQ2d 1294, 1298 (Fed. Cir. 1999).

Meyer teaches that, to effect a targeted sequence alteration,

> [c]ompositions of the invention include a modified oligonucleotide comprising an electrophilic group covalently attached to an oligonucleotide capable of sequence-specific interaction with a target sequence in a double-stranded DNA molecule.[2]
>
> An electrophilic group is a reagent or moiety that accepts an electron pair (from a nucleophilic group) to form a covalent bond.[3]
>
> After complex formation with the target sequence, the modified oligonucleotide is capable of reacting with the target DNA to form a covalent bond therewith. As a result of covalent bond formation between the modified ODN and the target sequence, replication and/or expression of the target sequence can be affected in such a way as to cause a heritable alteration in one or more nucleotides of the target sequence.[4]

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[2] Col. 4, lines 54-58.

[3] Col. 6, lines 40-42.

[4] Col. 5, lines 6-14.

Binding of a modified oligonucleotide of the invention to its target sequence places the attached electrophilic group in proximity to a functional group on an adjacent or nearby nucleotide. Such functional groups include, but are not limited to, the N3 and N7 atoms of guanine and adenine, the N1 atom of adenine, the N3 atom of cytosine and the O6 atom of guanine. When so positioned, the electrophilic group has a high probability of reacting with the functional group, thereby generating a potentially mutagenic lesion. In vivo, when the DNA comprising the potentially mutagenic lesion is subjected to cellular replication and/or repair processes, the lesion can become converted into a mutation. Mutation can occur in one of several ways: by a change in nucleotide sequence, by insertion, by deletion or by transposition.[5]

In order to achieve targeted modification at a specific sequence in a living cell, it is desirable to ensure that the majority of modified oligonucleotides that bind to a target sequence become covalently attached to that sequence. Since hybridization is a reversible process, it is necessary for reaction of the electrophilic group of the modified oligonucleotide to occur shortly after hybridization, and not be dependent on outside activation. Since the modified oligonucleotides of the present invention are inherently capable of forming crosslinks with their target sequences, exogenous activation of the reactive group is not required, as is the case with photoactivatible crosslinking agents. Hence, the method of the present invention does not require light or any other outside agent to

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[5] Col. 15, lines 57-59.

> facilitate crosslinking. Since crosslinking by the modified ODNs of the invention does not require external activation subsequent to formation of a triple-stranded complex between the mutagenic oligonucleotide of the invention and its target sequence, the majority of binding events will generate a crosslink. Consequently, the mutagenic efficiency of the method of the present invention is much higher than that of previous methods, in which only that fraction of the modified oligonucleotides that were bound to the target at the time the external activating stimulus was applied were capable of even potentially generating a mutation.[6]

Applicants respectfully submit that Meyer, which teaches the absolute requirement for a chemically reactive electrophilic crosslinking moiety to effect oligonucleotide-mediated sequence alteration, teaches away from combination with Yamamoto's unmodified oligonucleotides, vitiating the Examiner's *prima facie* case.[7] Applicants further submit that Meyer's requirement for an electrophilic crosslinking group on the sequence-altering oligonucleotide equally teaches away from applicants' claimed methods in which the sequence-altering oligonucleotides lack such chemically reactive crosslinking electrophilic moieties.

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[6] Col. 16, lines 16-38.

[7] Indeed, it would appear that even were combination permissible, the combination of Yamamoto with Meyer can yield nothing more than Meyer itself -- use of an oligonucleotide having reactive electrophilic groups -- which is demonstrably not applicants' invention.

Accordingly, applicants respectfully submit that the Examiner has failed to present a viable *prima facie* case, and further submit that any such *prima facie* case that might be deemed established has been fully rebutted. Applicants thus respectfully submit that the rejection should be withdrawn.

Yamamoto in View of Wengel

In a second rejection under 35 U.S.C. § 103, the Examiner rejects claims 25 - 30, 37, 38, 40, 44 - 47, and 53 - 62 over Yamamoto in view of Wengel. Claims 31 - 36, 41 - 43, 48 - 52, and 63 - 77 are free of this rejection.

Yamamoto teaches oligonucleotide-mediated nucleic acid sequence alteration using large amounts of unmodified oligonucleotides in yeast, a species known to be highly competent for recombination and repair. Wengel teaches a new class of modified nucleobase and oligonucleotides and polynucleotides that include such modified bases, termed locked nucleic acids (LNA).

The Examiner argues that motivation to include LNA modifications in the oligonucleotides of Yamamoto, thereby reconstructing the invention of certain of applicants' claims, may be found in Wengel's teaching "that the LNA modification improves the affinity and specificity of the oligonucleotide for its target sequence." Office action at 14 - 15.

Applicants respectfully disagree. As noted in applicants' specification:

> [a]lthough different modifications are known to have different effects on the nuclease resistance of oligonucleotides or stability of duplexes formed by such oligonucleotides (see, e.g., Koshkin et al., J. Am. Chem. Soc., 120:13252-3), we have found that it is not possible to predict which of any particular known modification would be most useful for any given alteration event, including for the construction of gene conversion oligonucleotides, because of the interaction of different as yet unidentified proteins during the gene alteration event.

Specification, page 5, lines 13 - 20. For example, applicants observe that

> [t]he efficiency of gene alteration is surprisingly increased with oligonucleotides having internal complementary sequence comprising phosphorothioate modified bases as compared to 2'-O-methyl modifications. This result indicates that specific chemical interactions are involved between the converting oligonucleotide and the proteins involved in the conversion. The effect of other such chemical interactions to produce nuclease resistant termini using modifications other than LNA, phosphorothioate linkages, or 2'-O-methyl analog incorporation into an oligonucleotide can not yet be predicted because the proteins involved in the alteration process and their particular chemical interaction with the oligonucleotide substituents are not yet known and cannot be predicted.

Specification, page 7, line 27 - page 8, line 3.

Wengel does not speak to the effects of LNA modifications on targeted sequence alteration reactions performed in the presence of, and mediated by, cellular repair

proteins, as claimed by applicants. Nor could he have so spoken, since the effects of such modifications could not have been predicted. For the same reason, there could not have been a reasonable expectation that such modification would have been effective in applicants' methods.

Applicants thus respectfully submit that the Examiner has failed to carry the twin burdens required to establish a viable *prima facie* case of obviousness.[8]

The PTO bears the initial burden of presenting a *prima facie* case of obviousness. When the PTO fails to meet its burden, an applicant is entitled, *without more*, to issuance of the patent. *In re Glaug*, 62 USPQ2d 1151, 1152 (Fed. Cir. 2002) (reversing the Board's holding of obviousness for failure to state an adequate *prima facie* case); *In re Oetiker*, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992) ("If examination at the initial stage does not produce a *prima facie* case of unpatentability, then without more the applicant is entitled to grant of the patent."); *In re Grabiak*, 769 F.2d 729, 733, 226 USPQ 870, 873 (Fed. Cir. 1985) ("On the record before us, we conclude that the PTO did not establish a *prima facie* case of obviousness, and thus did not shift to Grabiak the burden of coming forward with evidence of unexpected results").

Applicants respectfully submit that the rejection is in error and should be withdrawn.

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[8] "The consistent criterion for determination of obviousness is whether [i] the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and [ii] would have a reasonable likelihood of success." *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

Yamamoto in View of Barracchini

In a third rejection under 35 U.S.C. § 103, the Examiner rejects claims 25 - 30, 37, 38, 40, 44 - 47, 53 - 58 and 63 - 69 over Yamamoto in view of Barracchini.[9] Claims 63 - 77 are free of this rejection.

Barracchini teaches antisense oligonucleotides. The antisense oligonucleotide may include various "nucleobase . . . modifications or substitutions." Col. 7, lines 15 - 17 (described in detail thereafter). The oligonucleotide is completely complementary to its target.

The Examiner argues that Barracchini "teaches that therapeutic oligonucleotides comprising 2-O-Me or phosphorothioate modifications are preferable over native forms because of desirable properties such as, for example, enhanced cellular uptake, enhanced affinity or the target nucleic acid sequence, and increased stability in the presence of nucleases." Office action, 15 - 16. On that basis, the Examiner contends that Barracchini itself provides the motivation to combine its teachings with those of Yamamoto, and that there would have been a reasonable expectation of success in so doing.

Applicants disagree.

For the reasons advanced above, incorporated here by reference, the effect of such modifications on targeted

[9] Applicants understand the Examiner to have intended Barracchini in the sole reference to Wengel at item 17, page 15.

sequence alteration in the presence of cellular repair proteins was not, and could not, have been predicted, nor could any such modification have been attended by a reasonable expectation of success. Accordingly, applicants submit that the *prima facie* case rests upon faulty assumptions, must fail, and that the rejection should on that basis be withdrawn.

CONCLUSION AND REQUEST FOR TELEPHONIC INTERVIEW

Applicants respectfully submit that the claims are in good and proper form for allowance.

Applicants respectfully request that the Examiner grant a telephonic interview to the undersigned attorney of record if he believes that any matters remain outstanding before allowance of the claims.

Respectfully submitted,

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